REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The rejection of claims 41-52 and 78-83 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed.

The U.S. Patent and Trademark Office ("PTO") takes the position that the specification is lacking for not disclosing how to express the gene products of SEQ ID Nos. 1 and 2 in host cells. However, from page 17, line 1, to page 20, line 4, the specification discloses methods for introducing nucleic acid molecules into host cells and expressing the gene products. In particular, on page 17, lines 9-26, the specification teaches how to express sodium channel proteins in *Xenopus*. The reference cited in that section provides evidence of the state of the art at the time that the application was filed; i.e., that those of ordinary skill in the art could express functional foreign sodium channel proteins in host cells.

There is more than sufficient evidence in the specification to allow those of ordinary skill in the art to conclude that the disclosed proteins are functional sodium channel proteins. The sequences of the genes used in the present invention were determined from cDNA libraries, indicating that the genes are expressed in the cell. The proteins encoded by the genes have the conserved regions of known functional sodium channel genes. Moreover, a partial gene sequence was determined, which was then used to obtain the whole gene sequence. The partial gene sequence was from a gene which is tightly linked to an insecticide resistance trait (Knipple et al., "Tight Genetic Linkage Between the *kdr* Insecticide Resistance Trait and a Voltage-Sensitive Sodium Channel Gene in the House Fly," Proc. Nat'l Acad. Sci. USA, 91:2483-2487 (1994) ("Knipple")). Based upon the homology in the conserved regions, the tight linkage to the insecticide resistance, and the fact that the protein is expressed in cells, those of ordinary skill in that art would correlate the protein encoded by the gene sequence with a function of a sodium channel and insecticide resistance.

The PTO has taken the position that the methods of the present invention are contingent on the successful expression of the sodium channel proteins in appropriate host cells and that there is no evidence that successful and functional expression of the deduced

sodium channel proteins of SEQ. ID. Nos. 3 and 4, which are encoded by the nucleotide sequences of SEQ. ID. Nos. 1 and 2, respectfully, is possible. This concern is obviated by the results reported in the five references discussed below which demonstrate that functional expression of the subject sodium channel proteins can be achieved in accordance with the disclosure of the present application.

Smith et al., "The L1014F Point Mutation in the House Fly *Vssc1* Sodium Channel Confers Knockdown Resistance to Pyrethroids," Insect Biochem. Molec. Biol. 27(10):807-12 (1997) ("Smith I") (attached hereto as Exhibit 1) describes the functional expression in *Xenopus laevis* oocytes of the insecticide-susceptible wild type sodium channel as in SEQ. ID. No. 3 and of the insecticide-resistant mutant sodium channel with an L1014F point mutation as in SEQ. ID. No. 4. As described in the original application at page 17 and in accordance with techniques widely known in the relevant art, these sodium channel proteins were expressed by injecting *Xenopus* oocytes with aqueous solutions containing synthetic cRNA corresponding to the deduced sodium channel proteins. Smith I further demonstrates that the L1014F mutation contained in the resistance-associated sodium channel of SEQ. ID. No. 4, reduces the sensitivity of expressed sodium channels to the pyrethroid insecticide cismethrin.

Smith et al., "Actions of the Pyrethroid Insecticides Cismethrin and Cypermethrin on House Fly *Vssc1* Sodium Channels Expressed in *Xenopus* Oocytes," Archives of Insect Biochem. and Physiology 38:126-36 (1998) ("Smith II") (attached hereto as Exhibit 2) provides further evidence of the functional expression of the sodium channel protein of SEQ. ID. No. 3 in *Xenopus* oocytes. In Smith II, the house fly sodium channel protein of SEQ. ID. No. 3 was expressed in *Xenopus* oocytes in order to study the modification of sodium currents by cismethrin and cypermethrin. The method of expression used in Smith II was the same method as disclosed in the present application at page 17 and in Smith I.

Lee et al., "Mutations in the House Fly *Vssc1* Sodium Channel Gene Associated with *Super-kdr* Resistance Abolish the Pyrethroid Sensitivity of Vssc1/tipE Sodium Channels Expressed in *Xenopus* Oocytes," Insect Biochem. Molec. Biol. 29:185-94 (1999) ("Lee I") (attached hereto as Exhibit 3) further advances the studies of Smith I and Smith II with regard to the functional expression of the sodium channel protein of SEQ. ID.

No. 3. In particular, Lee I examines the impact of the M918T/L1014F double mutation associated with *super-kdr* resistance on the functional properties and pyrethroid sensitivity of Vssc1/tipE sodium channels expressed in oocytes. The principle finding of this study is that the M918T mutation eliminated the sensitivity of Vssc1/tipE sodium channels to pyrethroids.

Lee et al., "Cloning and Functional Characterization of a Putative Sodium Channel Auxiliary Subunit Gene from the House Fly (*Musca domestica*)," Insect Biochem. Molec. Biol. 30479-87 (2000) ("Lee II") (attached hereto as Exhibit 4) further demonstrates the functional expression of the sodium channel protein of SEQ. ID. No. 3. Specifically, Lee II teaches the isolation and cloning of a cDNA from the house fly encoding a tipE-like protein (designated Vsscβ) and demonstrates both the enhancement of Vssc1 sodium channel expression in oocytes and the modification of the kinetic properties of Vssc1 sodium channels by co-expression with Vsscβ.

Lee et al., "The V410M Mutation Associated with Pyrethroid Resistance in *Heliothis virescens* Reduces the Pyrethroid Sensitivity of House Fly Sodium Channels Expressed in *Xenopus* Oocytes," Insect Biochem. Molec. Biol. 31:19-29 (2001) ("Lee III") (attached hereto as Exhibit 5) describes the introduction of the V410M mutation into the wildtype house fly Vssc1 sodium channel by site-directed mutagenesis, the expression of functional wildtype and mutated channels in *Xenopus* oocytes, and the biophysical properties and sensitivity to cismethrin and BTX of the expressed channels. As with the references described above, Lee III demonstrates that house fly sodium channels can be functionally expressed in *Xenopus* oocytes in accordance with the disclosure of the present application. In particular, Lee III extends the work of the references cited above by taking advantage of the house fly sodium channel expression system to assess the effects of the V410M mutation, which is associated by both genetic and physiological criteria with *kdr*-like resistance in some populations of *Heliothis virescens*.

Thus, the attached articles demonstrate that the present application provides a fully enabling disclosure of how to achieve functional expression of the claimed sodium channel proteins. Therefore, the rejection under 35 U.S.C. § 112 (first paragraph) should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the foregoing, it is submitted that this case is in condition for allowance, and such allowance is earnestly solicited.

Respectfully submitted,

Date: February 9, 2001

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2/9/01	Jo Ann Whalen
Date	Jo Ann Whalen

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at line 8 of page 1 has been amended as follows:

This application is a divisional application of Serial No. 08/772,512, filed on December 24, 1996, **now U.S. Patent No. 6,022,705, issued on February 8, 2000,** which is a continuation-in-part of U.S. Serial No. 08/608,618, filed March 1, 1996, the contents of which are hereby incorporated by reference.